REMARKS

Claims 1-9 and 11-14 are under consideration. Claims 10 and 15-51 have been withdrawn from consideration.

Claims 1 and 12 are currently amended to require that the IRM compound is covalently bonded or attached via a high-affinity biotin linkage. Support for covalent bonding is throughout the application and original claims, while support for high-affinity attachment specifically using a biotin linker can be found at, e.g., page 28, lines 8-14, and examples 1 and 17.

35 USC 102 and 103 rejections

Covalent and biotin attachments vs. conventional mixtures

The present claims require attachment via covalent bonding or using biotin to make a high-affinity linkage between the IRM and macromolecular support. None of U.S. 4,689,338 (Gerster), U.S. 7,030,129 (Miller), and U.S. 6,894,060 (Slade) shows these kinds of chemical bond attachment to a solid support complex (gel, paste, and so on). Mere blending of the IRMs disclosed in Gerter, Miller and Slade with excipients to provide a gel, paste, or cream would not result in the formation of a covalent bond or a high-affinity non-covalent interaction.

In other words, the present claims would not read on a conventional gel formulation where the IRM is merely mixed in where weak hydrogen bonds may form, but would read on a gel formulation where the IRM is actually *covalently bonded* to the gel forming polymer itself. These are completely distinct compositions.

Accordingly, it is respectfully submitted that the amended claims are clearly novel and nonobvious over Gerster, Miller, and Slade.

35 USC 112 rejections

Applicants respectfully submit that there is a great deal of information in the disclosure specifically supporting the details of a wide range of covalent bonding chemistries according to the invention. There are also specific examples involving biotin-based high-affinity bonds.

Applicants' disclosure provides various possible reactive sites on the IRM compounds at which the IRM compound may be covalently linked to the substrate, a linking group, or a high-affinity functional group (e.g., avidin or biotin). (See, Formula I, page 32, and page 34, lines 17

and 18) The IRM reactive site selected for any one embodiment is *independent* of the particular macromolecular support material being used.

The reactive sites of macromolecular support materials are also well known. While the reactive site of a gel may, indeed, be somewhat different than the reactive site on a bead, these differences are known, e.g., through literature provided by manufacturers of commercially available support materials. Moreover, the reaction schemes necessary to attach molecules at these reactive sites on macromolecular support materials are also known.

Formation of covalent bonds

As described in the specification (page 28 line 30 through page 34 line 20) and demonstrated in the examples an IRM can be covalently attached to a macromolecular support material by reacting a functional group on the IRM with a functional group on the macromolecular support material to form a covalent bond. As disclosed in the specification, many functionalized IRMs are known. Numerous macromolecular support materials containing functional groups are commercially available. Others can be readily prepared using known methods; for example, glass can be treated with a silane coupling agent.

In Examples 2 – 11, an IRM containing a triethoxysilyl group was reacted with SiO_2 (silica) particles to provide an IRM-support complex in which the IRM is covalently attached to the silica particle through the formation of an oxane bond (silica-0-Si-IRM). As demonstrated in the Examples (pages 37- 38) IRMs containing a triethoxysilyl group can be readily prepared from known IRM compounds and commercially available heterobifunctional linkers in which one of the functional groups is a triethoxysilyl group. SiO_2 particles are commercially available in a range of sizes. One of ordinary skill in the art understands that treating an aqueous dispersion of silica at an elevated temperature with a compound containing a triethoxysilyl group would result in the formation of oxane bonds.

An oxane bond was also formed in Example 13 when an IRM containing a triethoxysilyl group was reacted with a triethoxysilane grafted fluoropolymer film.

An oxane bond was also formed in Example 21 when an IRM containing a triethoxysilyl group was reacted with commercially available silica coated supermagnetic particles.

In Example 21, an IRM containing a triethoxysilyl group was reacted with commercially available iron oxide particles to provide an IRM-support complex in which the IRM is covalently attached to the iron oxide particle through the formation of an oxane bond (Fe-O-Si-IRM). Iron oxide particles are commercially available in a range of sizes.

In Examples 27 – 29, an IRM containing an aminoalkyl group was reacted with oxirane functionalized acrylic beads to provide an IRM-support complex in which the IRM is covalently attached to the bead through the formation of an amino alcohol (bead-CH_2(OH)-CH_2-NH-IRM). IRMs containing an alkylamino group are known. Oxirane functionalized beads are commercially available. One of ordinary skill in the art understands that the reaction of an oxirane with an alkylamine would result in the formation of an amino alcohol.

An amino alcohol was also formed in Example 19 when an IRM containing an aminoalkyl group was reacted with commercially available epoxy functionalized supermagnetic particles. One of ordinary skill in the art understands that the reaction of an epoxide with an alkylamine would result in the formation of an amino alcohol.

In Examples 30 – 31, an IRM containing an aminoalkyl group was reacted with carboxylate functionalized polystyrene beads to provide an IRM-support complex in which the IRM is covalently attached to the bead through the formation of an amide bond (bead-C(O)-NH-IRM). The carboxylate group was activated with EDC. IRMs containing an alkylamino group are known. Carboxylate functionalized beads are commercially available. Use of EDC to activate a carboxylate group is well known. One of ordinary skill in the art understands that the reaction of an alkylamine with an activated acid would result in the formation of an amide bond.

An amide bond was also formed in Examples 15 and 16 when an IRM containing an aminoalkyl group was reacted with carbonate functionalized gold particle. The carbonate group was activated with EDC.

An amide bond was also formed in Example 18 when an IRM containing a carboxyl group was reacted with ferritin. The carboxyl group on the IRM was activated with EDC and the activated group reacted with a primary amine on the ferritin.

An amide bond was also formed in Example 23 when an IRM containing an aminoalkyl group was reacted with human serum albumin. A carboxylate group on the human serum albumin was activated with EDC.

An amide bond was also formed in Example 24 when an IRM containing an aminoalkyl group was reacted with collagen fibers. A carboxylate group on the collagen was activated with 1,3-dicyclohexylcarbodiimide.

An IRM-support complex in which the IRM is covalently attached to a bioadhesive polymer through the formation of an amide bond could be prepared as described in Example 22 by reacting an IRM containing an aminoalkyl group with a free carboxylic acid group on a bioadhesive crosslinked polymer of acrylic acid. Bioadhesive crosslinked polymers of acrylic acid are commercially available.

Formation of a high-affinity non-covalent attachment

As described in the specification (page 27 line 23 through page 28 line 29) and demonstrated in the examples an IRM can be non-covalently attached to a macromolecular support material by use of the well-known biotin-avidin interaction. The biotin-avidin complex is the strongest known non-covalent protein-ligand interaction.

In Example 1 two different IRMs each containing a biotin moiety were coupled to immobilized monomeric avidin beads and to immobilized tetrameric avidin beads. Some IRMs containing a biotin moiety are known (U.S. Patent 6,451,810). As demonstrated in the Examples (Preparation of IRM2 on page 36), others can be readily prepared from known IRM compounds and commercially available linkers containing a biotin moiety at one end and a functional group at the other. Macromolecular supports containing immobilized avidin are commercially available.

In Example 17 an IRM was coupled to gold particles using an IRM containing a biotin moiety and commercially available gold-streptavidin.

The Office Action also states (page 5 of the office action), "Glassy and ceramic compounds are not known to easily for[m] a covalent bond with compounds." Applicants respectfully disagree. Those skilled in the art possess significant knowledge regarding the attachment of molecules to glassy and ceramic substrates; see, e.g., U.S. Patent No. 6,582,938

(e.g., col. 9, lines 24-33) and U.S. Patent Publication No. 2002/0022721 A1 (paragraphs 0114 and 0131 through 0134) and patent documents cited therein.

It is well known that the silanol groups (Si-OH) which are present on the surface of glass under go condensation reactions with silane coupling agents to form oxane bonds. Numerous silane coupling agents are known and permit the covalent attachment of a variety of functional groups, such as, for example, amines, mercaptans, and halides to glass. These functional groups can then be reacted with functional groups on the IRM to provide covalent bonds.

Applicants respectfully submit that macromolecular support material reactive sites for the full scope encompassed by the claims have been properly enabled. Withdrawal of the section 112, first paragraph, rejection is therefore requested.

CONCLUSION

In view of the above, Applicants submit that claims 1 to 9 and 11 to 14 are allowable. Reconsideration of the application is requested.

Allowance of claims 1 to 9 and 11 to 14 at an early date is solicited.

Respectfully submitted,

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